Docket No. 10806-106

PATENT

CERTIFICATE OF MAILING

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, DC 20231 on January 7, 2002.

Holly D Kozlowski

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Johan Stjernschantz et al	:	Paper No.:
Serial No.:	09/445,919	:	Group Art Unit: 1614
Filed:	March 16, 2000	:	Examiner: Z. Fay

For: **Prostaglandin Derivatives Devoid of Side-Effects for the Treatment of Glaucoma**

TRANSMITTAL OF APPEAL BRIEF

Assistant Commissioner for Patents
Washington, DC 20231

Dear Sir:

Submitted herewith in **triplicate** is an Appeal Brief in support of the Notice of Appeal filed by Certificate of Mailing on September 6, 2001 and received by the U.S. Patent and Trademark Office on September 10, 2001. The government fee in the amount of $320.00 for filing the present Appeal Brief is enclosed by check.

Please charge any additional fees required or credit any excess in fees paid in connection with the present communication to Deposit Account No. 04-1133.

Respectfully submitted,

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APPEAL BRIEF

Assistant Commissioner for Patents
Washington, DC 20231

Dear Sir:

The present Appeal Brief is submitted in support of the Notice of Appeal filed by Certificate of Mail on September 6, 2001 and received by the U.S. Patent and Trademark Office on September 10, 2001.

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is the assignee of the present application, Pharmacia & Upjohn AB, now, by change of name, Pharmacia AB.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellants, the Appellants' undersigned legal representative or the assignee which will directly effect or be directly effected by or having a bearing on the Board's decision in the present appeal.

III. STATUS OF THE CLAIMS

Claims 4-11 and 18-23 are pending and stand rejected. Claims 1-3 and 12-17 have been cancelled. A copy of the pending claims is set forth in the Appendix.

IV. STATUS OF AMENDMENT FILED SUBSEQUENT TO FINAL REJECTION

An Amendment Under 37 C.F.R. 1.116 is submitted herewith. In the Amendment, claims 1-3 and 13-17 are cancelled, claims 4 and 5 are presented in independent form, and the dependency of claims 18-21 is corrected, in order to reduce the issues on appeal. The Appendix submitted herewith incorporates the amendments set forth in the Amendment Under 37 C.F.R. 1.116. In the event that the Examiner does not enter the Amendment Under 37 C.F.R. 1.116, a revised Appendix will be provided.

V. SUMMARY OF THE INVENTION

The present invention is directed to compositions and methods for the treatment of glaucoma and/or ocular hypertension.

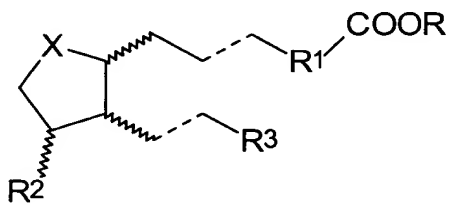
According to independent claim 4, the composition for the treatment of glaucoma and ocular hypertension comprises a therapeutically active and physiologically acceptable amount of a prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, or a pharmaceutically acceptable salt or ester thereof, wherein the prostaglandin analogue is 15(R,S)-16,16-trimethylene-PGE_2 or an alkyl ester thereof.

According to independent claim 5, the composition for the treatment of glaucoma and ocular hypertension comprises a therapeutically active and physiologically acceptable amount of a prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, or a

pharmaceutically acceptable salt or ester thereof, wherein the prostaglandin analogue is 13,14-dihydro-17-(3-fluorophenyl)-18,19,20-trinor-PGE_2 or an alkyl ester thereof.

According to independent claim 6, the invention is directed to a method of treating glaucoma or ocular hypertension in a subject's eye. The method comprises contacting the surface of the eye with an effective intraocular pressure reducing amount of therapeutically active and physiologically acceptable prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, or a pharmaceutically acceptable salt or ester thereof.

Claims 7-11 and 18-21 further define the methods of claim 6. According to claim 7, the prostaglandin analogue is derived from PGF or PGE prostaglandins. According to claim 8, the prostaglandin analogue is a compound of the general formula:



wherein the wavy bonds represent the α or β configuration, and the dashed bonds represent a single bond, a triple bond or a double bond in the cis or trans configuration;

R is hydrogen, saturated or unsaturated alkyl, cycloalkyl, aryl, arylalkyl, or heteroaryl;

R1 is a saturated or unsaturated alkyl group having 2-5 carbon atoms, optionally interrupted by one or more heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, cycloalkyl, cycloalkenyl, aryl or heteroaryl;

X is C-OH or C=O;

R2 is hydrogen, hydroxy, methyl, ethyl, methoxy or OCOR4, where R4 is a straight or branched chain saturated or unsaturated alkyl group, or a cycloalkyl or aryl group; and

R3 is a straight or branched chain saturated or unsaturated alkyl group, optionally interrupted by one or more heteroatoms selected from the group consisting of oxygen, sulfur

and nitrogen, each carbon atom optionally being substituted with a substituent selected from C_{1-5} alkyl, hydroxy and carbonyl groups, and said alkyl group optionally containing a cycloalkyl, aryl or heteroaryl group, optionally mono-or independently multi-substituted with C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy, nitro, trifluoromethyl or halogen;

or a pharmaceutically acceptable salt or ester thereof.

Claim 18 recites that R is C_{1-10} alkyl, C_{3-8} cycloalkyl or aryl-C_{2-5} alkyl. Claim 19 recites that R1 is C_{3-7} cycloalkyl or C_{3-7} cycloalkenyl. Claim 20 recites that R2 is hydrogen, hydroxy, methyl, ethyl, methoxy or OCOR4, wherein R4 is C_{1-10} alkyl or C_{3-8} cycloalkyl. Claim 21 recites that R3 is a straight or branched chain saturated or unsaturated alkyl group having 3-8 carbon atoms, optionally interrupted by one or more heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, each carbon atom optionally substituted with a substituent selected from C_{1-5} alkyl, hydroxy and carbonyl groups, wherein the hydroxy and carbonyl are attached to carbon 15 of the prostaglandin structure, and said alkyl group optionally containing a C_{3-8} cycloalkyl, optionally mono- or independently tri-substituted with C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy, nitro, trifluoromethyl or halogen.

According to claim 9, the prostaglandin analogue is 15(R,S)-16,16-trimethylene-PGE_2 or an alkyl ester thereof, while according to claim 10, the prostaglandin analogue is 13,14-dihydro-17-(3-fluorophenyl)-18,19,20-trinor-PGE_2 or an alkyl ester thereof.

According to claim 11, a therapeutically active and physiologically acceptable composition containing said prostaglandin analogue is administered topically on the eye 1-3 times daily.

According to independent claim 22, the invention is directed to a method of treating glaucoma or ocular hypertension in a subject's eye while reducing melanogenesis. The method comprises contacting the surface of the eye with an effective intraocular pressure reducing amount of a therapeutically active and physiologically acceptable prostaglandin

analogue which is a selective agonist for EP_1 prostanoid receptors, or a pharmaceutically acceptable salt or ester thereof. Any melanogenesis which is caused by the method of treatment is reduced as compared with that obtained by a method of treatment in which a prostaglandin analogue which is not a selective agonist for EP_1 prostanoid receptors is employed.

Finally, claim 23 recites that in the method according to claim 22, melanogenesis is avoided.

VI. ISSUE ON APPEAL

The single issue presented on appeal for review by the Board is the rejection of claims 4-11 and 18-23 under 35 U.S.C. §103 as being unpatentable over the published PCT International application WO 94/08585 and the Kluender et al U.S. Patent No. 4,132,738.

VII. GROUPING OF THE CLAIMS

With respect to the above-noted issue on appeal, Appellants submit that independent claims 4, 5, 6 and 22 are each independently patentable. Appellants further submit that claims 9 and 10 are independently patentable from claim 6 from which they depend and that claim 23 is independently patentable from claim 22 from which it depends. Reasons in support of the independent patentability of these claims are set forth below.

VIII. ARGUMENTS

As will be set forth in detail below, Appellants submit that the compositions defined by claims 4 and 5 and the methods defined by claims 6-11 and 18-23 are nonobvious over and patentably distinguishable from the published PCT International application WO 94/08585 (WO '585) and the Kluender et al U.S. Patent No. 4,132,738 (Kluender et al).

Accordingly, the rejection under 35 U.S.C. §103 should be reversed. Favorable action by the Board is respectfully requested.

A. The Examiner's Position

In rejecting the claims as being unpatentable over WO '585 and Kluender et al, the Examiner asserted that WO '585 teaches the use of prostaglandin E and F in a pharmaceutical composition for the treatment of glaucoma and that Kluender et al teach the use of the claimed prostaglandins in a pharmaceutical formulation. The Examiner stated that claims are directed to the use of specific prostaglandin E and F for the treatment of glaucoma but asserted that it would have been obvious to use derivatives of prostaglandin E and F for the treatment of glaucoma in the absence of evidence to the contrary. The Examiner relied on *In re Dillon*, 16 U.S.P.Q.2d 1897, 1900 (Fed. Cir. 1990) for the proposition that the recitation of a new utility for an old and well known composition does not render the composition new, and the Examiner asserted that Appellants have presented no evidence to establish an unexpected or unobvious nature of the claimed invention.

B. Composition Claims 4 and 5 are Patentable Over WO '585 and Kluender et al

Independent claims 4 and 5 are directed to compositions for the treatment of glaucoma and ocular hypertension. These compositions comprise a therapeutically active and physiologically acceptable amount of a prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, or a pharmaceutically acceptable salt or ester thereof. According to claim 4, the prostaglandin analogue is 15(R,S)-16,16-trimethylene-PGE_2 or an alkyl ester thereof. Compounds 5 and 6 as set forth in Scheme 1 on page 26 of the present application are within the scope of claim 4. According to claim 5, the prostaglandin analogue is 13,14-dihydro-17-(3-fluorophenyl)-18,19,20-trinor-PGE_2 or an alkyl ester thereof. Compound 7 as set forth in Scheme 1 on page 26 of the present application is within the scope of claim 5.

It is well known that the practical usefulness of many prostaglandins and their derivatives as suitable drugs for treatment of glaucoma or ocular hypertension is limited by the tendency of these compounds to cause increased pigmentation of the iris in the eye, causing the iris to become dark brown, as discussed in the specification in the paragraph bridging pages 4 and 5. Appellants have unexpectedly found that compositions containing the specific prostaglandin analogues of claims 4 and 5, which are selective agonists for the EP_1 subgroup of prostanoid receptors, may be used to effectively reduce intraocular pressure in the treatment of glaucoma or ocular hypertension without increased, or with significantly reduced, melanogenesis, i.e., darkening of the iris.

WO '585 discloses the use of a combination of at least one clonidine derivative and at least one prostaglandin for treating glaucoma and ocular hypertension to reduce the inflammatory response typically found with prostaglandins (page 3, lines 4-7). At pages 7-10, WO '585 discloses various prostaglandin compounds which may be employed. However, Appellants find no teaching or suggestion in WO '585 of compositions containing the prostaglandin analogue 15(R,S)-16,16-trimethylene-PGE_2, or an alkyl ester thereof, as required in the compositions of claim 4. Similarly, Appellants find no teaching or suggestion in WO '585 of the prostaglandin analogue 13,14-dihydro-17-(3-fluorophenyl)-18,19,20-trinor-PGE_2, or an alkyl ester thereof, as required in the compositions of claim 5. The broad teachings of WO '585 relating to various prostaglandin compounds do not teach or suggest the specific prostaglandin analogues employed in the compositions of claim 4 or claim 5. Similarly, Appellants find no teaching, suggestion or recognition of the ability of any prostaglandin compounds to act as a selective agonist for EP_1 prostanoid receptors, relating to compositions containing a selective agonist for EP_1 prostanoid receptors, or relating to any advantage provided by such compositions.

Kluender et al disclose the preparation of 15-deoxy-16-hydroxy prostaglandins of the formula set forth at columns 7-8. However, one skilled in the art will easily recognize that the prostaglandin compounds taught by Kluender et al are different from the prostaglandin analogues employed in the compositions of claims 4 and 5. Appellants find no teaching or suggestion by Kluender et al for modifying any of the compounds disclosed therein to result in the prostaglandin analogues employed in the compositions of claims 4 and 5.

The Examiner relies on *In re Dillon, supra*, to assert that the recitation of a new utility for an old and well-known composition does not render that composition new. However, the Examiner has not established on the record that the compositions of claims 4 and 5 are old and well known. Thus, the Examiner's reliance on *In re Dillon, supra*, is misplaced.

References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, 203 U.S.P.Q. 245 (CCPA 1979). Appellants find no teaching in the cited references relating to prostaglandin analogues as employed in the compositions of claims 4 and 5. Similarly, Appellants find no teaching or suggestion in the cited references relating to the use of such prostaglandin analogues in a composition for the treatment of glaucoma and ocular hypertension that such analogues are selective agonists for EP_1 prostanoid receptors. Thus, WO '585 and Kluender et al do not provide an enabling disclosure of the compositions of claim 4 or claim 5 and therefore do not place the claimed compositions in the possession of the public. Accordingly, WO '585 and Kluender et al do not support a rejection of claim 4 or claim 5 under 35 U.S.C. §103. The rejection of these claims should therefore be reversed.

C. Method Claims 6-11 and 18-23 are Patentably Distinguishable from WO '585 and Kluender et al

According to independent claim 6, the methods of the invention are directed to treating glaucoma or ocular hypertension in a subject's eye and comprise contacting the

surface of the eye with an effective intraocular pressure reducing amount of a therapeutically active and physiologically acceptable prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, or a pharmaceutically acceptable salt or ester thereof. According to independent claim 22, the methods of the invention are directed to the treatment of glaucoma or ocular hypertension in a subject's eye while reducing melanogenesis. The methods comprise contacting the surface of the eye with an effective intraocular pressure reducing amount of a therapeutically active and physiologically acceptable prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, or a pharmaceutically acceptable salt or ester thereof, wherein any melanogenesis which is caused by the method of treatment is reduced as compared with that obtained by a method of treatment in which a prostaglandin analogue which is not a selective agonist for EP_1 prostanoid receptors is employed.

As noted above, WO '585 discloses the use of at least one clonidine derivative and at least one prostaglandin to treat glaucoma and ocular hypertension. However, Appellants find no teaching, suggestion or recognition in WO '585 of prostaglandin analogues which are selective agonists for EP_1 prostanoid receptors, or that the use of selective agonists for EP_1 prostanoid receptors is advantageous. Particularly, Appellants find no teaching, suggestion or recognition in WO '585 of a method of treating glaucoma or ocular hypertension in a subject's eye employing selective agonists for EP_1 prostanoid receptors as recited in claim 6. Similarly, Appellants find no teaching, suggestion or recognition in WO '585 of a method of treating glaucoma or ocular hypertension in a subject's eye while reducing melanogenesis, as recited in claim 22.

The deficiencies of WO '585 are not resolved by Kluender et al. As discussed above, Kluender et al disclose the preparation of 15-dioxy-16-hydroxyprostaglandins. Kluender et al disclose that the prostaglandins produce bronchodilation and decreased gastric secretion *in vivo*. However, Appellants find no teaching or suggestion by Kluender et al relating to a

method for treating glaucoma or ocular hypertension in a subject's eye as recited in claim 6, a method of treating glaucoma or ocular hypertension in a subject's eye while reducing melanogenesis as recited in claim 22, or relating to prostaglandin analogues which are selected agonists for EP_1 prostanoid receptors or the use of such selective agonists for treating glaucoma or ocular hypertension in a subject's eye. The teaching by Kluender et al relating to hydroxyprostaglandins for bronchodilation and gastric secretion reduction are simply not relevant to the presently claimed methods and do not resolve any of the deficiencies of WO '585.

In the Official Actions, the Examiner asserted that there is no evidence of record to demonstrate the reduced melanogenesis. Appellants submit that the Examiner is mistaken. That is, the Board's attention is directed to the specification at pages 9-12 wherein Appellants disclose their discovery that human iridial melanocytes show an expression of FP, EP_2 and EP_3 receptors, but do not show the presence of EP_1 and TP receptors. As the human iridial melanocytes do not exhibit EP_1 receptors, one skilled in the art will appreciate that the present methods employing a selective agonist for EP_1 prostanoid receptors will not result in the increased melanogenesis obtained upon use of prostaglandin analogues which are not a selective agonist for EP_1 prostanoid receptors. Moreover, at pages 23-26 of the present application, Appellants demonstrate that the selective agonists for EP_1 prostanoid receptors are effective for treating glaucoma or ocular hypertension in a subject's eye. Thus, the present specification clearly demonstrates to one of ordinary skill in the art the advantages of the claimed methods of treating glaucoma or ocular hypertension in a subject's eye while reducing melanogenesis as compared with that obtained by a method of treatment in which a prostaglandin analogue which is not a selective agonist for EP_1 prostanoid receptors is employed.

In view of the failure of WO '585 and Kluender et al to teach or suggest methods of treating glaucoma or ocular hypertension in a subject's eye by contacting the surface of the eye with a prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, and the failure of these references to teach, suggest or recognize a method of treating glaucoma or ocular hypertension in a subject's eye while reducing melanogenesis, WO '585 and Kluender et a do not provide an enabling disclosure of the presently claimed methods and do not place these methods in the possession of the public. Thus, WO '585 and Kluender et al do not support a rejection under 35 U.S.C. §103, *In re Payne, supra*. It is therefore submitted that the rejection of method claims 6-11 and 18-23 should be reversed. Reconsideration is respectfully requested.

D. Claims 9 and 10 are Independently Patentable

The methods of claims 9 and 10 are further patentably distinguishable from WO '585 and Kluender et al. These claims depend from claim 6 and further specify that the prostaglandin analogue is 15(R,S)-16,16-trimethylene-PGE2 or an alkyl ester thereof (claim 9) or is 13,14-dihydro-17-(3-fluorophenyl)-18,19,20-trinor-PGE2 or an alkyl ester thereof (claim 10). As discussed in detail above, Appellants find no teaching or suggestion by WO '585 or Kluender et al of the prostaglandin analogue 15(R,S)-16,16-trimethylene-PGE_2, or an alkyl ester thereof, or of the prostaglandin analogue 13,14-dihydro-17-(3-fluorophenyl)-18,19,20-trinor-PGE_2, or an alkyl ester thereof. Accordingly, Appellants find no teaching or suggestion by WO '585 or Kluender et al of a method of treating glaucoma or ocular hypertension in a subject's eye by contacting the surface of the eye with an effective intraocular pressure reducing amount of the prostaglandin analogue 15(R,S)-16,16-trimethylene-PGE_2, or an alkyl ester thereof, or of the prostaglandin analogue 13,14-dihydro-17-(3-fluorophenyl)-18,19,20-trinor-PGE_2. Similarly, Appellants find no teaching, suggestion or recognition by WO '585 or Kluender et al that such prostaglandin analogues are

selective agonists for EP_1 prostanoid receptors, or that such methods provide therapeutic results with reduced melanogenesis.

In view of these deficiencies in the teachings of WO '585 and Kluender et al, these references do not provide an enabling disclosure of the methods of claim 9 or 10 and do not place the inventions of claim 9 or 10 in the possession of the public. Thus, WO '585 and Kluender et al do not support a rejection of claim 9 or claim 10 under 35 U.S.C. §103, *In re Payne, supra*. The rejection of claims 9 and 10 under 35 U.S.C. §103 should therefore be reversed.

E. Claim 23 is Independently Patentable

The methods of claim 23 are further patentably distinguishable from WO '585 and Kluender et al. This claim depends from claim 22 and further specifies that melanogenesis is avoided. Appellants find no teaching or suggestion by WO '585 or Kluender et al of a method of treating glaucoma or ocular hypertension in a subject's eye while reducing melanogenesis by contacting the surface of the eye with an effective intraocular pressure reducing amount of a prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, wherein melanogenesis is avoided. In fact, Appellants find no teaching, suggestion or recognition by either of the cited references that melanogenesis can be avoided in any prostaglandin treatment, or that melanogenesis can be avoided by a method employing a selective agonist for EP_1 prostanoid receptors.

In view of these deficiencies in the teachings of WO '585 and Kluender et al, these references do not provide an enabling disclosure of the methods of claim 23 and do not place the invention of claim 23 in the possession of the public. Thus, WO '585 and Kluender et al do not support a rejection of claim 23 under 35 U.S.C. §103, *In re Payne, supra*. The rejection of claim 23 under 35 U.S.C. §103 should therefore be reversed.

IV. CONCLUSIONS

For the reasons set forth in detail above, the compositions defined by claims 4 and 5 and the methods defined by claims 6-11 and 18-23 are nonobvious over and patentably distinguishable from the published PCT International application WO 94/08585 and the Kluender et al U.S. Patent No. 4,132,738. Accordingly, the rejection under 35 U.S.C. §103 should be reversed. Favorable action by the Board is respectfully requested.

Respectfully submitted,

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APPENDIX

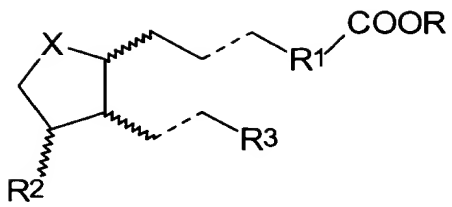
4. A composition for the treatment of glaucoma and ocular hypertension comprising a therapeutically active and physiologically acceptable amount of a prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, or a pharmaceutically acceptable salt or ester thereof, wherein the prostaglandin analogue is 15(R,S)-16,16-trimethylene-PGE_2 or an alkyl ester thereof.

5. A composition for the treatment of glaucoma and ocular hypertension comprising a therapeutically active and physiologically acceptable amount of a prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, or a pharmaceutically acceptable salt or ester thereof, wherein the prostaglandin analogue is 13,14-dihydro-17-(3-fluorophenyl)-18,19,20-trinor-PGE_2 or an alkyl ester thereof.

6. A method of treating glaucoma or ocular hypertension in a subject's eye, which method comprises contacting the surface of the eye with an effective intraocular pressure reducing amount of therapeutically active and physiologically acceptable prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, or a pharmaceutically acceptable salt or ester thereof.

7. The method according to claim 6, wherein the prostaglandin analogue is derived from PGF or PGE prostaglandins.

8. The method according to claim 6, wherein the prostaglandin analogue is a compound of the general formula:



wherein:

the wavy bonds represent the α or β configuration, and the dashed bonds represent a single bond, a triple bond or a double bond in the cis or trans configuration;

R is hydrogen, saturated or unsaturated alkyl, cycloalkyl, aryl, arylalkyl, or heteroaryl;

R1 is a saturated or unsaturated alkyl group having 2-5 carbon atoms, optionally interrupted by one or more heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, cycloalkyl, cycloalkenyl, aryl or heteroaryl;

X is C-OH or C=O;

R2 is hydrogen, hydroxy, methyl, ethyl, methoxy or OCOR4, where R4 is a straight or branched chain saturated or unsaturated alkyl group, or a cycloalkyl or aryl group; and

R3 is a straight or branched chain saturated or unsaturated alkyl group, optionally interrupted by one or more heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, each carbon atom optionally being substituted with a substituent selected from C_{1-5} alkyl, hydroxy and carbonyl groups, and said alkyl group optionally containing a cycloalkyl, aryl or heteroaryl group, optionally mono-or independently multi-substituted with C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy, nitro, trifluoromethyl or halogen;

or a pharmaceutically acceptable salt or ester thereof.

9. The method according to claim 6, wherein the prostaglandin analogue is 15(R,S)-16,16-trimethylene-PGE_2 or an alkyl ester thereof.

10. The method according to claim 6, wherein the prostaglandin analogue is 13,14-dihydro-17-(3-fluorophenyl)-18,19,20-trinor-PGE_2 or an alkyl ester thereof.

11. The method according to claim 6, wherein a therapeutically active and physiologically acceptable composition containing said prostaglandin analogue is administered topically on the eye 1-3 times daily.

18. The method according to claim 8, wherein R is C_{1-10} alkyl, C_{3-8} cycloalkyl or aryl-C_{2-5} alkyl.

19. The method according to claim 8, wherein R1 is C_{3-7} cycloalkyl or C_{3-7} cycloalkenyl.

20. The method according to claim 8, wherein R2 is hydrogen, hydroxy, methyl, ethyl, methoxy or OCOR4, wherein R4 is C_{1-10} alkyl or C_{3-8} cycloalkyl.

21. The method according to claim 8, wherein R3 is a straight or branched chain saturated or unsaturated alkyl group having 3-8 carbon atoms, optionally interrupted by one or more heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, each carbon atom optionally substituted with a substituent selected from C_{1-5} alky, hydroxy and carbonyl groups, wherein the hydroxy and carbonyl are attached to carbon 15 of the prostaglandin structure, and said alkyl group optionally containing a C_{3-8} cycloalkyl, optionally mono- or independently tri-substituted with C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy, nitro, trifluoromethyl or halogen.

22. A method of treating glaucoma or ocular hypertension in a subject's eye while reducing melanogenesis, which method comprises contacting the surface of the eye with an effective intraocular pressure reducing amount of a therapeutically active and physiologically acceptable prostaglandin analogue which is a selective agonist for EP_1 prostanoid receptors, or a pharmaceutically acceptable salt or ester thereof, any melanogenesis which is caused by the method of treatment being reduced as compared with that obtained by a method of treatment in which a prostaglandin analogue which is not a selective agonist for EP_1 prostanoid receptors is employed.

23. The method according to claim 22, wherein melanogenesis is avoided.